1

General introduction.

INTRODUCTION IN VASCULITIS

The systemic vasculitides are rare inflammatory diseases characterized by inflammation of blood vessel walls, possible in any part of the body (1-6). There are several different types of vasculitis. There is an infectious vasculitis where invasion and proliferation of pathogens in vessel walls results directly in inflammation. Another kind is secondary vasculitis, referring to vasculitis that is associated with divers aetiologies like reaction to drugs or chemicals or often occurring as a consequence of other illnesses such as cancer or systemic diseases like rheumatoid arthritis or lupus vasculitis (2,4,6).
Less common are the primary systemic vasculitides, i.e. idiopathic forms, not known to be caused by direct vessel wall invasion by pathogens or related to obvious reasons.
During the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis in 1994, revised in 2012, an attempt was made to distinguish the primary vasculitides according to vessel wall size into large-vessel-, medium sized-, and small vessel vasculitis (6). The extent of the vasculitis may account for partial stenosis of larger vessels but may also lead to complete stenosis of medium and small arteries, veins and capillaries; the other way around, it may also lead to minor or serious bleeding complications (6). This is important for diagnosis, treatment, but also for the prognosis. Because of the possibility of damage to vessel walls throughout the whole body, the primary systemic vasculitides can affect various organs and the different forms of vasculitis can cause different damage: some are relatively mild and require no treatment, while the other type of disease can cause severe and serious illnesses or even death if not diagnosed promptly and treated appropriately (6).
The large- and medium sized vessel vasculitis are beyond the scope of this thesis; all of the following is focused on small vessel vasculitis.

The small vessel vasculitides can be divided into those associated with antineutrophil cytoplasmic antibody (ANCA) and those not associated with ANCA (6).
ANCA are auto-antibodies that recognize neutrophil and monocyte constituents, the main targets being proteinase 3 (PR3) and myeloperoxidase (MPO); it is estimated that PR3-ANCA and MPO-ANCA are found in >90% of patients with ANCA-associated vasculitis (AAV) (7-10).
Strong in vivo evidence that at least MPO-ANCA is pathogenic was achieved with the development of the first mouse model in which injection of MPO-ANCA induced glomerulonephritis and vasculitis comparable to human disease (11,12). However, this is not reproduced in models that use PR3-ANCA as antigen. Maybe this is one of the reasons that there are meaningful clinical differences, for instance in disease spectrum, between patients with PR3-AAV and with MPO-AAV (6,7,13). In general, patients with PR3-ANCA have more widespread extrarenal organ involvement and more active lesions at time of

presentation, compared to MPO-ANCA who have more chronic lesions. Another important difference is the higher relapse rate in PR3-ANCA positive patients (7,14-16).

Patients suffering from ANCA-associated vasculitis may present with a rapid clinical decline due to life threatening progressive loss of renal or respiratory function, but as mentioned before, the organs that can be affected are widespread. Since the disease can affect various organs, the symptoms can easily be confused with other illnesses (5). Because of this potential rapid deterioration, once suspected, a prompt diagnosis of AAV may lead to instalment (or well based abstention in case of a high probability of a differential diagnosis) of appropriate and effective therapy and maybe could reverse a potential fatal outcome.

The disease can usually be controlled by use of steroids and immunosuppressive drugs, although there is no definite cure for AAV (17,18). Due to the frequent occurrence of relapses, long term maintenance therapy is often required. Induction treatment as well as maintenance therapy are accompanied by serious side effects and although the combined treatment modalities have turned these progressive and often fatal diseases into chronic conditions, mortality and morbidity are substantial, either due to disease itself or the toxicity of prolonged courses of immunosuppressive treatment (17,19).

AIMS AND OUTLINE OF THE THESIS.

This thesis focuses on improving outcome by methods to recognize and correctly diagnose the disease as soon as AAV is suspected. Furthermore, an attempt has been made to identify parameters for prognosis and relapse risk. Knowing these parameters, a proposal for tailor-made therapy is defined to potentially reduce the well-known toxicity of induction treatment, long-term maintenance therapy and especially the re-instalment of aggressive treatment for relapses.
Hopefully, this proposal will enable treating physicians to make a well-funded choice in immunosuppression, leading to a better quality of life and longer life expectancy for individualized ANCA-associated vasculitis patients.

Part 1 of this thesis focuses on tools for prompt diagnosis, with emphasis on the diagnostic performance of two rapid ANCA- and anti-GBM test methods, Dotblot and Phadia ELiA (chapter 2). Furthermore, in chapter 3, predictors for patient and renal survival at diagnosis and after induction therapy in ANCA-associated vasculitis with and without renal involvement are evaluated. In chapter 4, we describe a stepwise immunosuppressive approach, i.e adding plasmapheresis relatively late after diagnosis, in 26 AAV-patients to standard induction therapy in 50 comparable controls. In chapter 5, characteristics of stabilization and remission of renal involvement are described.

Part 2 starts with a full review of all aspects on maintenance therapy with emphasis on relapses and risk factors. Recommendations for choice of agent and duration of maintenance therapy are made for different patient groups and a flow chart for maintenance therapy is added (chapter 6).
In the next two chapters, azathioprine as maintenance agent is evaluated in a national study as well as in a large international cohort. Chapter 7 describes the results of a prospective multicentre clinical trial ('AZA-ANCA' trial), set up to evaluate efficacy and safety of extended azathioprine maintenance therapy in patients with PR3-AAV. The choice for extension of maintenance therapy was based on a retrospective national study which showed that patients with PR3-ANCA who remained c-ANCA positive during treatment, were significantly more prone for relapse during long-term follow up.
In chapter 8, we studied whether in AAV-patients the duration of azathioprine maintenance therapy influenced relapse rate during long-term follow up. For this chapter, we were enabled by European Vasculitis Study Group (EUVAS) and French Vasculitis Study Group (FVSG) to study and evaluate the treatment characteristics and results of 6 international and large studies on AAV-patients.

Finally, in chapter 9, the results of our studies are summarized and they are put into perspective. This is also the place for speculation on future developments.

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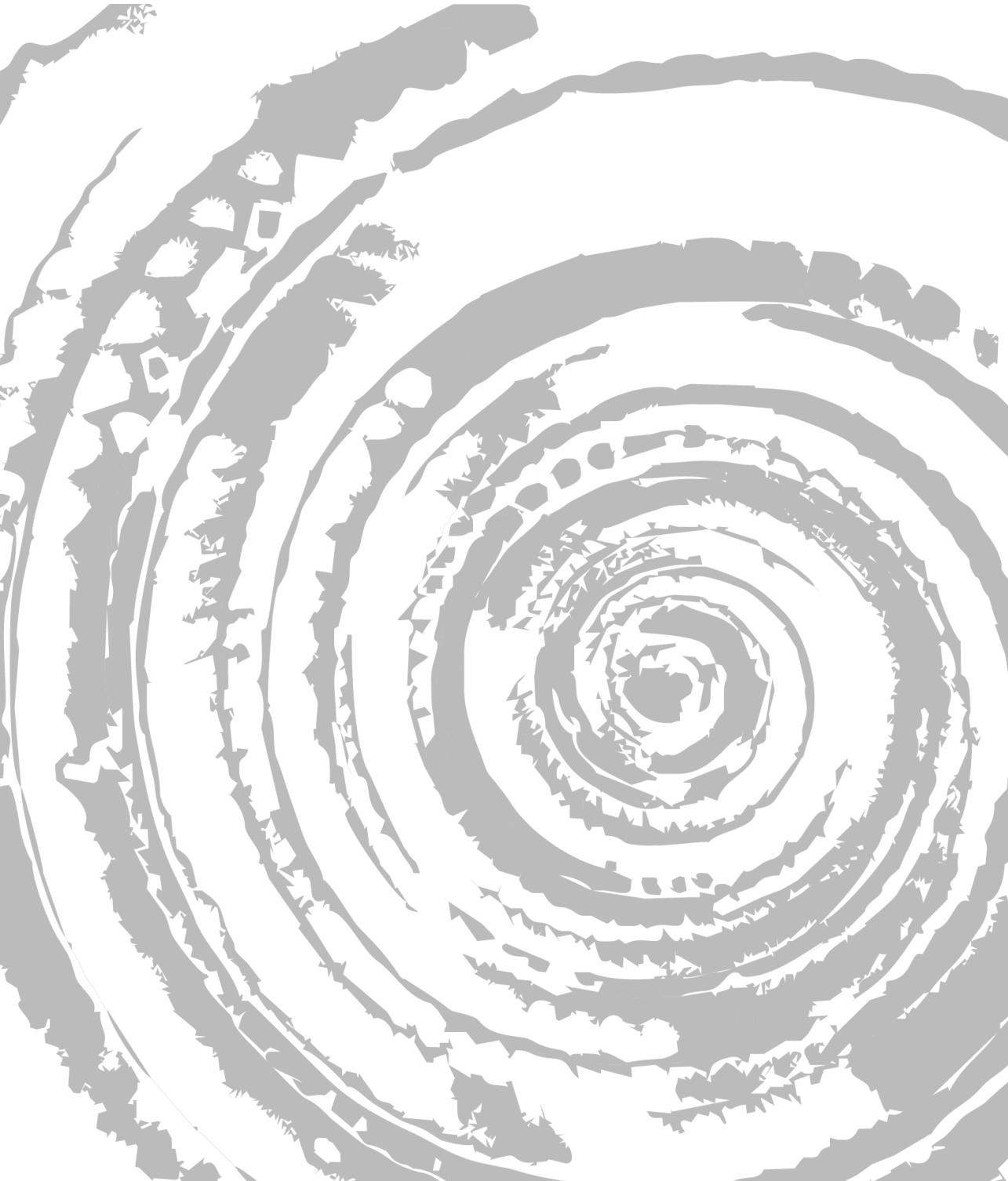
19. Wall N, Harper L. Complications of long term therapy for ANCA-associated vasculitis. Nat Rev Nephrol 2012;8:523-532.Chapter 8: summary, general discussion and future perspectives



PART 1